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Long-Term Follow-Up of a Pediatric Cohort With Short QT Syndrome

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Objectives The purpose of this study was to define the clinical characteristics and long-term follow-up of pediatric patients with short QT syndrome (SQTS).

Background SQTS is associated with sudden cardiac death. The clinical characteristics and long-term prognosis in young patients have not been reported.

Methods This was an international case series involving 15 centers. Patients were analyzed for electrocardiography characteristics, genotype, clinical events, Gollob score, and efficacy of medical or defibrillator (implantable cardioverter-defibrillator [ICD]) therapy. To assess the possible prognostic value of the Gollob score, we devised a modified Gollob score that excluded clinical events from the original score.

Results Twenty-five patients 21 years of age or younger (84% males, median age: 15 years, interquartile range: 9 to 18 years) were followed up for 5.9 years (interquartile range: 4 to 7.1 years). Median corrected QT interval for heart rate was 312 ms (range: 194 to 355 ms). Symptoms occurred in 14 (56%) of 25 patients and included aborted sudden cardiac death in 6 patients (24%) and syncope in 4 patients (16%). Arrhythmias were common and included atrial fibrillation (n = 4), ventricular fibrillation (n = 6), supraventricular tachycardia (n = 1), and polymorphic ventricular tachycardia (n = 1). Sixteen patients (84%) had a familial or personal history of cardiac arrest. A gene mutation associated with SQTS was identified in 5 (24%) of 21 probands. Symptomatic patients had a higher median modified Gollob score (excluding points for clinical events) compared with asymptomatic patients (5 vs. 4, p = 0.044). Ten patients received medical treatment, mainly with quinidine. Eleven of 25 index cases underwent ICD implantation. Two patients had appropriate ICD shocks. Inappropriate ICD shocks were observed in 64% of patients.

Conclusions SQTS is associated with aborted sudden cardiac death among the pediatric population. Asymptomatic patients with a Gollob score of <5 remained event free, except for an isolated episode of supraventricular tachycardia, over an average 6-year follow-up. A higher modified Gollob score of 5 or more was associated with the likelihood of clinical events. Young SQTS patients have a high rate of inappropriate ICD shocks. (J Am Coll Cardiol 2013;61:1183–91) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ECG = electrocardiography
ICD = implantable cardioverter-defibrillator
IQR = interquartile range
QTc = corrected QT interval for heart rate using the Bazett formula
SCD = sudden cardiac death
SQTS = short QT syndrome
SVT = supraventricular tachycardia
VF = ventricular fibrillation

The short QT syndrome (SQTS) is a primary cardiac electrical disease and one of the recent additions of inherited arrhythmias associated with sudden cardiac death (SCD). Although believed to be a rare condition, the entire disease spectrum continues to emerge with newly recognized cases, and as we continue to understand the disease better and to characterize it more fully, a broader disease spectrum may be revealed. The underlying pathophysiological features involve shortening of myocardial repolarization, which creates the electrical substrate for atrial and ventricular tachyarrhythmias (1). The arrhythmogenic potential of a short QT interval was described first by Gussak et al. (2). To date, genetic studies have shown that SQTS is associated with gain-of-function mutations in 3 different potassium channels (3–6) and 3 loss-of-function mutations in the L-type cardiac calcium channel, although forms of short QT interval associated with calcium channelopathies show phenotypic overlap with Brugada syndrome (7,8).

In SQTS, the corrected QT interval for heart rate using the Bazett formula (QTc) in most reported cases to date usually is <340 to 360 ms, with rare exceptions (9). A normal QT interval has been reported as 370 ± 30 ms in children (10) and 385 ± 24 ms in adults (11), with a slightly longer QT interval in post-pubescent females (12). According to population studies (13), a QTc interval of 340 to 360 ms has been proposed as the lower limit of normal. However, as demonstrated with long QT syndrome, there is an overlapping range of QT intervals between affected individuals (14) and apparently healthy subjects (15). It is likely SQTS cases with longer QTc interval exist. In contrast, the presence of a short QT interval in isolation may not always be indicative of SQTS. Thus, Gollob et al. (16) proposed diagnostic criteria for SQTS (Table 1).

The therapeutic approach to SQTS is not well defined. An implantable cardioverter-defibrillator (ICD) may be considered as primary therapy, given the known risk of SCD (17). However, the risk-to-benefit ratio of such an approach remains unknown, particularly in the young. Although hydroquinidine has demonstrated some benefit in a limited number of patients (18,19), there is limited experience with medical therapy.

To date, the long-term prognosis in young SQTS patients has not been reported. We set out to define the clinical characteristics and long-term outcomes of a pediatric cohort diagnosed with SQTS.

Methods

Study population. Pediatric SQTS patients (≤21 years of age at clinical presentation) from 15 centers in North and South America, Europe, and Japan were characterized clinically and were followed up beginning in 2007. Entry criteria included: 1) QT interval of 330 ms or less; or 2) QTc interval of 360 ms or less with 1 or more of the following: syncope, atrial fibrillation, ventricular fibrillation (VF), aborted SCD, positive family history of SQTS or unexplained SCD, or a combination thereof. A total of 28 patients were enrolled, of whom 25 met the inclusion criteria for this study: 1) a Gollob diagnostic score of 3 or more (indicating a moderate to high probability of SQTS); and 2) clinical follow-up longer than 1 year. Patient demographic data were collected. The ECG parameters analyzed included: QT interval, QTc interval, J point-to-T peak interval, and early repolarization. The QT interval was measured manually. The QTc interval was calculated using Bazett's formula. The J point was defined as the end of the QRS interval and the beginning of the ST segment. The T peak was measured at the highest point of the T-wave. Early repolarization was defined as an elevation of more than 0.1 mV of the J point from baseline in at least 2 contiguous

Table 1 SQTS Diagnostic Criteria: Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: ≤2 points. Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history events must occur in the absence of an identifiable cause, including structural heart disease. Points can be received only for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history points can only be received once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

QTc = corrected QT interval for heart rate using the Bazett formula; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.

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Table 2 SQTS Diagnostic Criteria: Modified Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Family history points can be received only once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

Abbreviations as in Table 1.

leads in the inferior leads (II, III, aVF), lateral leads (I, aVL, V_4 to V_6), anterior leads (V_1 to V_3), or combinations thereof. The contour of the ST segment was classified as having either upsloping or horizontal (downsloping) morphological features. Patients with ICD were assessed for implant indication, delivered therapies, and device complications. We elected to explore the risk-stratifying value of specific variables within the Gollob scoring system. Thus, the diagnostic Gollob score was modified, by excluding clinical events, into a new prognostic score referred to as the modified Gollob score (Table 2).

Statistical analysis. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]: 25th to 75th percentile). Analyzed continuous variables are presented only as medians with IQR and were analyzed using the Wilcoxon rank sum test. Categorical variables are presented as counts with percentages and were analyzed using the Fisher exact test or the chi-square test. Correlation between continuous data was analyzed using the Spearman correlation coefficient. Two-tailed p values of <0.05 were considered statistically significant. Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Clinical data. There were 25 patients and a total of 21 (84%) were male. Their clinical data are presented in Table 3. Patients were followed up for a median of 5.9 years (IQR: 4 to 7.1 years). Patient age at the time of clinical presentation ranged from 1 day to 21 years (13.4 ± 6 years, median: 15 years, IQR: 9 to 18 years), with 9 patients (36%) younger than 12 years.

ECG. The QT interval varied from 160 to 360 ms (279 ± 51 ms, median: 290 ms, IQR: 280 to 300 ms), whereas the QTc interval ranged from 194 to 355 ms (304 ± 41 ms, median: 312 ms, IQR: 286 to 335 ms). The J point-to-T peak interval ranged from 63 to 180 ms (132 ± 35 ms, median: 140 ms, IQR: 119 to 160 ms). Arrhythmias were common: 4 patients had atrial fibrillation, 6 had VF, and 1 had supraventricular tachycardia (SVT) at presentation.

GENETIC TESTING. Genetic testing was undertaken in 21 of the 25 patients, and 5 patients had a confirmed mutation. All gene-positive patients were symptomatic, including a 3-month-old young female with recurrent atrial fibrillation since the age of 4 days and associated sinus and atrioventricular node dysfunction (KCNQ1 V141M). Tables 3 and 4 outline the culprit genes, specific mutations, and associated symptoms and arrhythmias detected in the gene-positive cohort.

FAMILY HISTORY. A personal or familial history of cardiac arrest was present in 16 (84%) of 25 patients. A familial history of SCD, presumed to be arrhythmogenic, was present in 5 symptomatic patients and in 6 asymptomatic patients. These involved 6 siblings (4 young males and 2 young females), 2 uncles, and 1 father. The equal distribution of familial SCD among symptomatic and asymptomatic individuals suggests that SCD alone may not predict prognosis, although numbers were relatively small in this study. Among the entire cohort, there was a positive family history for a clinical diagnosis of SQTS in 17 (68%) patients, equally distributed between parents and siblings. Among the patients with atrial fibrillation, only 1 of 4 had a family history of atrial fibrillation. In the patients with VF, only 1 of 6 had a first-degree relative (father) with SCD. Overall, the prevalence of symptomatic family members did not seem to be more common in symptomatic patients, although a much larger cohort would be required to assess confidently whether a symptomatic family member predicts individual risk. Only 4 of 25 patients had no family history of SQTS or SCD.

Symptomatic versus asymptomatic patients. Of the entire cohort, 14 (56%) patients had 1 or more clinical features associated with SQTS, including aborted SCD in 6 (24%), unheralded syncope in 4 (16%), and palpitations with documented atrial fibrillation in 4 (16%). The remaining 11 (44%) patients were asymptomatic, 10 of whom were identified through family screening and the remaining through an incidental ECG finding of a very short QTc interval (292 ms). There was no significant difference in median age between symptomatic and asymptomatic patients (median: 15 years, IQR: 8 to 17 years vs. median: 17 years, IQR: 9 to 18 years, $p = 0.621$). All but 1 of the asymptomatic cases had a family history of SQTS or unexplained SCD.

ECG PARAMETERS. No differences were found in the ECG parameters between asymptomatic and symptomatic patients (Table 3). Although the QTc interval tended to be shorter in symptomatic patients (median: 306 vs. 330 ms), the difference was not statistically significant ($p = 0.207$).

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Table 3 Characteristics of All Patients

Variable	Total (n = 25)	Symptomatic* (n = 14)	Asymptomatic (n = 11)	p Value
Patient age at presentation (yrs)	15 (9–18)	15 (8–17)	17 (9–18)	0.621
Age <12 yrs	9 (36%)	4 (28.6%)	5 (45.5%)	0.434
Male	21 (84%)	11 (78.6%)	10 (90.9%)	0.604
Follow-up duration (yrs)	5.9 (4.4–7.1)	5.7 (4.8–7.4)	6.1 (3.2–6.9)	0.460
Symptoms				
Aborted SCD	6 (24%)	6 (43%)	—	
Unheralded syncope	4 (16%)	4 (28.5%)	—	
Palpitations†	4 (16%)	4 (28.5%)	—	
Modified Gollob score	5 (4–5)	5 (4–6)	4 (4–5)	**0.044**
Genetic mutation				
KCNH2	2 (8%)	2 (14%)	0	
KCNJ2	2 (8%)	2 (14%)	0	
KCNQ1	1 (4%)	1 (7%)	0	
ECG parameters				
QT (ms)	290 (280–300)	280 (200–300)	295 (280–320)	0.333
QTc (ms)	312 (286–335)	306 (252–329)	330 (292–335)	0.207
J point-to-T peak interval (ms)	140 (119–160)	130 (80–160)	140 (120–160)	0.344
J point-to-T peak interval <120 (ms)	7 (28%)	6 (42.9%)	1 (9.1%)	0.090
Early repolarization	12/24 (50%)	6/14 (43%)	6/10 (60%)	0.680
Family history				0.620
SQTS	8 (32%)	4 (28.6%)	4 (36.4%)	
SCD	4 (16%)	3 (21.4%)	1 (9.1%)	
SCD and SQTS	9 (36%)	4 (28.6%)	5 (45.5%)	
Negative	4 (16%)	3 (21.4%)	1 (9.1%)	
ICD	11 (44%)	8 (57.1%)	3 (27.3%)	0.227
Appropriate shocks	2 (18%)	2 (25%)	0	
Inappropriate shock	7 (63.6%)	4 (50%)	3 (100%)	
Complications‡	9 (81.8%)	6 (75%)	3 (100%)	

Values are median (interquartile range) or n (%). *Only patients with aborted sudden cardiac death, syncope, or documented ventricular or atrial fibrillation at presentation or during follow-up were considered symptomatic for short QT syndrome. †Palpitations and atrial fibrillation or supraventricular tachycardia. ‡Including inappropriate shocks.

ECG = electrocardiography; ICD = implanted cardiac defibrillator; J point-to-T peak interval = interval in milliseconds measured on standard electrocardiography ECG from the J-point to the peak T-wave voltage; SCD = sudden cardiac death. Other abbreviations as in Table 1.

There was a trend toward a higher prevalence of short J point-to-T peak interval (<120 ms) in the symptomatic versus the asymptomatic patients (42.9% vs. 9.1%, p = 0.090). Only 1 of the asymptomatic patients had a short J point-to-T peak interval. The presence of early repolarization did not differ between symptomatic and asymptomatic patients. Early repolarization was found in the anterior (n = 2), anterolateral (n = 2), lateral (n = 1), and anteroinferolateral (n = 1) leads in 43% of symptomatic cases. In 60% of asymptomatic cases, early repolarization was found in the inferolateral (n = 3) cases and in the anterior or lateral leads, or both (n = 3). In all cases, early repolarization had an upsloping ST segment pattern (Fig. 1).

GOLLOB DIAGNOSTIC SCORE FOR SQTS. Asymptomatic patients had Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher Gollob scores ranging from 4 to 10 (median: 6, IQR, 6 to 8, p < 0.001).

A modified Gollob score, excluding clinical events, was assigned to each patient. Asymptomatic patients had modified Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher scores ranging from 3 to 8 (median: 5, IQR: 4 to 6, p = 0.044).

ABORTED SCD. Aborted SCD occurred in 6 (24%) of 25 patients. These patients had a longer follow-up duration

Table 4 Genetic Mutations in the Pediatric Cohort

Age (yrs)	Sex	Gene	Mutation	Current	Symptoms	Arrhythmias
3	F	KCNQ1	V141M	IKs	None	Atrial fibrillation, sinus, and atrioventricular node dysfunction
5	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
8	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
14	M	KCNH2	N588K	IKr	Syncope	Ventricular fibrillation
19	M	KCNH2	E50D	IKr	Syncope	None

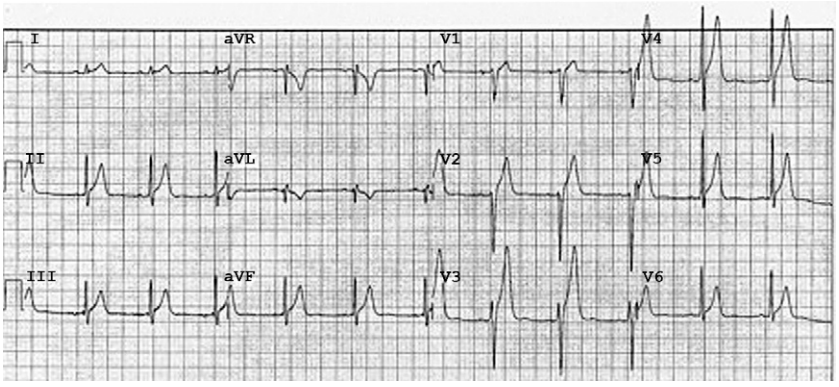

Figure 1 **Representative 12-Lead Electrocardiogram of the Short QT Syndrome**

Resting electrocardiogram (ECG) of a 15-year-old young male with aborted sudden cardiac death and a short QT interval (QT interval: 280 ms, QT interval corrected for heart rate [QTc]: 325 ms). There are peaked T waves in most of the precordial leads. The J point-to-T peak interval is 140 ms. There is early repolarization with upsloping ST segment in II, III aVF, and V_2 to V_6.

than those without aborted SCD (median: 7.3 years, IQR: 6.3 to 7.8 years vs. median: 5.3 years, IQR: 4.0 to 6.9 years, p = 0.045). A short J point-to-T peak (<120 ms) was more prevalent among the aborted SCD group (67% vs. 16%, p = 0.032) (Table 5). Five of these 6 patients had implantation of an ICD. In one instance, the parents declined an ICD for a 6-month-old young male (at the time of clinical presentation) with an ultra-short QT interval of 160 ms (QTc interval: 241 ms) who, at 80 months of follow-up, had no recurrent symptoms (Fig. 2). A positive family history of SQTS or SCD did not discriminate between aborted SCD and nonaborted SCD patients because of the high prevalence among the entire cohort. Early repolarization with upsloping ST segment in the anteroinferolateral leads was present in only 1 of the 6 patients with aborted SCD.

Therapy. ICD. Implantation of a cardioverter-defibrillator (ICD) was performed in 11 (44%) of 25 patients, in 6 as primary prevention (unexplained syncope in 2). Indications for ICD in the other 5 patients were aborted SCD or VF. Two (18%) patients had appropriate shocks: a 14-year-old young male (QT interval: 300 ms, QTc interval: 286 ms) with a history of aborted SCD while receiving quinidine at 9 mg/kg daily and a 14-year-old young male (QT interval: 248 ms; QTc interval: 252 ms) with a history of syncope and VF. The latter had no recurrent ICD appropriate shocks while taking quinidine. Two other patients had no shock and 7 (64%) had 1 or more inappropriate shocks. The underlying cause of inappropriate shocks was atrial fibrillation with rapid ventricular conduction (n = 1), sinus tachycardia (n = 3), SVT (n = 1), and ventricular lead fracture (n = 3), including 1 Sprint Fidelis lead (Medtronic, Minneapolis, Minnesota). There was an additional patient with a ventricular lead fracture 6 years after implantation that did not cause an inappropriate ICD shock. Of patients who received an ICD as primary prevention, 4 had inappropriate shocks.

MEDICAL THERAPY. Medical therapy was initiated in 10 (40%) of 25 patients, 4 of whom received multiple agents. Of the 4 patients with paroxysmal atrial fibrillation, 3 received quinidine therapy that proved unsuccessful in preventing recurrences of the arrhythmia. These patients were quite young, including an infant who also had recurrences while receiving propafenone and sotalol, a 5-year-old in whom flecainide also failed, and an 8-year-old. The remaining patient with atrial fibrillation was a 17-year-old young male (QT interval: 320 ms, QTc interval: 355 ms) (Fig. 3A) who was cardioverted at the time of ICD implantation, but continued to experience recurrences despite therapy with digoxin and propafenone. On treatment with digoxin and dofetilide, there was prolongation of the QT interval and return to sinus rhythm without symptomatic recurrences through follow-up (Fig. 3B). However, ICD interrogation identified asymptomatic, short episodes of atrial fibrillation. Two patients with a history of appropriate ICD shocks also received quinidine therapy. The first patient, a 14-year-old young male with aborted SCD, had a therapeutic shock while receiving quinidine 9 mg/kg daily. We were unable to confirm whether lack of compliance was the issue. The J point-to-T peak interval in this patient was 118 ms. He had a Gollob score of 8 with a QT interval of 300 ms (QTc interval: 286 ms). Genetic testing did not identify any known mutation. The second patient had no recurrent shocks while receiving quinidine therapy.

ARRHYTHMIAS ENCOUNTERED DURING FOLLOW-UP. Of the asymptomatic patients, only a 21-year-old man with an ICD as primary prevention had SVT resulting in inappropriate shocks and requiring ICD reprogramming. He had a modified Gollob score of 4. The other 10 asymptomatic cases with Gollob scores of 3 to 5 remained asymptomatic and arrhythmia-free during follow-up. In the group that was symptomatic at presentation, a 19-year-old man receiving no

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Table 5 Comparison of Patients With Versus Without Aborted Sudden Cardiac Death

Variable	Aborted SCD (n = 6)	No Aborted SCD (n = 19)	p Value
Patient age at presentation (yrs)	14 (14–15)	17 (8–18)	0.632
Age <12 yrs	1 (16.7%)	8 (42.1%)	0.364
Male	6 (100%)	15 (79%)	0.540
Follow-up duration (yrs)	7.3 (6.3–7.8)	5.3 (4.0–6.9)	0.045
Genetic mutation (n = 21)			
KCNH2	1 (20%)	1 (6.3%)	
KCNJ2	0	2 (12.5%)	
KCNQ1	0	1 (6.3%)	
Negative	4 (80%)	12 (75%)	
Family history			
SCD and/or SQTS	5 (83.3%)	16 (84.2%)	0.999
ECG parameters			
QT interval (ms)	280 (248–300)	295 (280–320)	0.261
QTc interval (ms)	300 (252–325)	312 (291–335)	0.323
QTc interval < 330 ms	5 (83.3%)	11 (57.9%)	0.364
J point-to-T peak interval	109 (80–140)	140 (120–160)	0.130
J point-to-T peak interval <120 ms	4 (66.7%)	3 (15.8%)	0.032
Early repolarization	1/6 (17%)	11/18 (61%)	0.155
Medical therapy with quinidine	3 (50%)	6 (31.6%)	0.344
Documented arrhythmia on follow-up			
Ventricular fibrillation	1 (16.7%)	0	
Polymorphic VT	1 (16.7%)	0	
Atrial fibrillation	0	3 (15.8%)	
SVT	0	1 (5.3%)	
ICD	5 (83.3%)	6 (31.6%)	0.056
Appropriate shocks	2 (40%)	0	
Inappropriate shock	3 (60%)	4 (66.7%)	
Complications*	5 (100%)	4 (66.7%)	

Values are median (interquartile range) or n (%). *Including inappropriate shocks.
SVT = supraventricular tachycardia; other abbreviations as in Tables 1 and 3.

medical therapy and with a history of aborted SCD experienced 2 episodes of nonsustained polymorphic ventricular tachycardia that terminated spontaneously. All cases with atrial fibrillation required ongoing therapy with cardioversion, medical treatment with different antiarrhythmic agents, or both. A 3-month-old young female with an ultra-short QT of 200 ms (QTc interval: 275 ms) had a history of marked sinus bradycardia since birth and atrioventricular node dysfunction with a Wenckebach cycle length of 500 ms. The patient demonstrated atrial fibrillation at 4 days of age, requiring cardioversion. A ventricular pacemaker was implanted at 6 days of age. Despite antiarrhythmic therapy, it eventually progressed into permanent atrial fibrillation. A 5-year-old young female with an ultra-short QT of 172 ms (QTc interval: 194 ms) had mechanically induced atrial and VF during insertion of a Swan Ganz catheter.

Discussion

To our knowledge, this is the longest follow-up cohort of patients with SQTS reported in the literature. It also represents the largest series of pediatric SQTS patients, because the average age in this cohort was 13 years.

Our cohort was predominantly male (84%), reflecting a sex-specific prevalence and possible greater vulnerability to SQTS in young males as compared with young females. Eighty-four percent of patients had a personal or familial history of cardiac arrest. More than half of our patients had symptoms, including aborted SCD (24%) and syncope (16%). The most common symptomatic presentation was cardiac arrest. An additional 11 cases (44% of cohort) were identified through cascade family screening. Twenty percent of cases were identified to have disease-causing mutations. Our cohort included a 6-year-old young male with aborted SCD and a QT interval of 160 ms, the shortest QT interval reported to date. In addition, we report 3 children younger than 8 years with recalcitrant atrial fibrillation and ultra-short QT intervals ranging from 172 to 200 ms and 1 patient, an infant with a QT of 200 ms (QTc interval: 275 ms), who had coexisting sinus and atrioventricular node dysfunction. This patient had sinus bradycardia at birth and demonstrated slow atrial fibrillation at 4 days of age. To our knowledge, the latter clinical scenario associated with a V141M mutation in the KCNQ1 gene has not been reported with SQTS. Another unique finding in this young population has been the high incidence of inappropriate shocks, affecting 64% of ICD recipients, which far exceeded appropriate shocks.

A previously reported study presented the clinical characteristics and outcomes in an adult population of SQTS patients (median age: 26 years) (19). Similar to the observations of our pediatric cohort, most clinically affected adults were men (75%), cardiac arrest as a first presentation was relatively common (32%), a family history of SQTS was present in 50% of patients, and disease-causing mutations were found in 23% of probands. In contrast, our pediatric cohort tended to have a shorter QTc interval (average: 304 ms vs. 314 ms), and although adult and pediatric ICD recipients both received a high inappropriate shock rate, this was more common in pediatric patients (64% vs. 33%).

Gollob et al. (16) proposed diagnostic criteria for SQTS. We found that a modified Gollob score, which excluded points for clinical events, may be useful in identifying patients at a higher risk for unexplained syncope, atrial fibrillation, or aborted SCD. Our patients with a history of these clinical events had a median modified score of 5 (range: 4 to 6) as compared with a median of 4 (range: 4 to 5) in patients who remained asymptomatic (except 1 case of SVT). Patients with a modified Gollob score of 3 (or Gollob score of <5) had a good prognosis during follow-up in this study. Only 1 (7%) of 14 symptomatic patients had a low modified Gollob score of 3.

SQTS is considered a rare electrical abnormality, and recognition of this condition as a cause of unexplained SCD in young children is uncommon, although perhaps underrecognized. A reported series of adult patients with idiopathic VF were noted to have a mean QTc value of 371 ms, significantly less than the QTc value of healthy sex- and age-matched controls (20). These observations suggest that

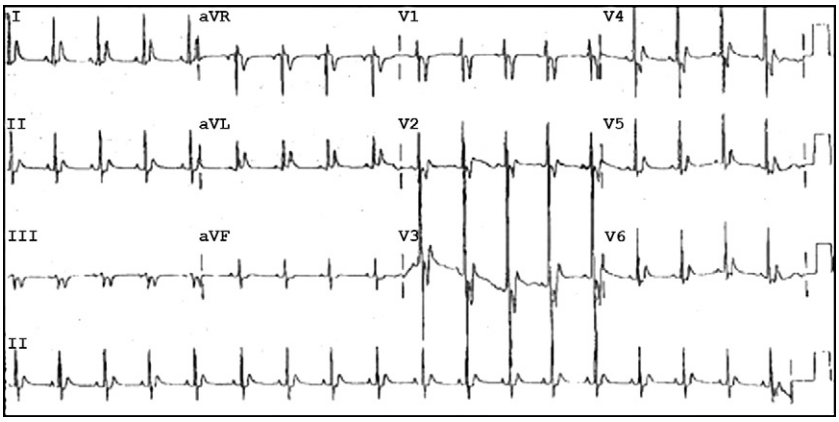

Figure 2 **Extreme Abbreviation of QT Interval in a Young, Symptomatic Child**

An ultra-short QT interval of 160 ms (QTc interval: 241 ms) in a 6-month-old young male at the time of clinical evaluation after cardiac arrest.

less extreme values of short QTc interval may be part of the SQTS disease spectrum.

Aborted SCD affected 6 of our patients (24%), 5 of them at 15 years of age or younger. One of the current therapeutic options for patients with SQTS includes implantation of an ICD (21–23). Six of our patients received an ICD for primary prevention; however, 4 experienced 1 or more inappropriate ICD shocks. Previous studies have reported an increased risk for inappropriate ICD therapy because of oversensing of short-coupled and prominent T waves resulting in T-wave oversensing (24). In our young cohort with SQTS, inappropriate shocks far exceeded appropriate shocks. Most of our patients had inappropriate shocks secondary to atrial tachycardias, including sinus tachycardia (n = 3), SVT (n = 1), and atrial fibrillation (n = 1). Inappropriate therapies resulting from rapid atrial arrhythmias may be prevented by programming device therapies for heart rates exceeding 210 beats/min, although a formative assessment is needed to evaluate the efficacy of such an approach. In addition, we observed a high prevalence of ventricular lead fracture of 36% (4 of 11 cases) with most (3 of 4) resulting in inappropriate ICD shocks. The high prevalence of ventricular lead fracture in part may be the result of the patients' young ages at implantation. These points together highlight our concerns regarding the use of ICD therapy in asymptomatic young patients.

We identified a higher prevalence of short J point-to-T peak interval (<120 ms) in symptomatic (42.9%) versus asymptomatic patients (9.1%). However, because of the small number of cases, the difference did not reach statistical significance. Watanabe et al. (25) reported a high prevalence (65%) of early repolarization in patients with SQTS that was associated with arrhythmic events. In their cohort, early repolarization was localized in either inferior leads, lateral leads, or both, but the ST segment contour was not described in their paper. Early repolarization with upsloping morphological features can be a benign ECG finding (26), whereas a horizontal or downsloping ST segment may be associated with VF (27). Early repolarization also was observed in a high percentage of our cohort (50%), and it was localized in anterior, inferior, and lateral leads, or in a combination thereof. This ECG feature was not significantly different between our symptomatic (43%) and asymptomatic (60%) patients. None of our patients with early repolarization had a horizontal or downsloping pattern. Only 1 of our 6 cases of aborted SCD showed early repolarization.

Five of our patients, all symptomatic, had genetic mutations associated with SQTS. The yield of genetic mutation detection was 24% for index patients who underwent genetic testing. This compares with the 23% incidence reported in the literature (16).

Quinidine has been suggested as one of the mainstay therapies for SQTS because of its ability to offset the extreme shortening of repolarization that occurs in SQTS (28). In this cohort, quinidine proved ineffective in managing atrial fibrillation in those patients with frequent recurrences. In addition, while receiving a low dose of quinidine, one patient experienced a therapeutic ICD shock. Therefore, the effectiveness of this antiarrhythmic agent in young SQTS patients awaits further investigation.

Study limitations. Although we describe the largest population of pediatric patients with SQTS with the longest reported clinical follow-up, event rates and risks in later decades of life remain unknown. As a relatively rare or perhaps under-recognized disease, our cohort included only 25 patients. Thus, we must be cautious in reaching conclusions based on such a small group.

Conclusions

SQTS in the pediatric population is associated with a high risk of aborted SCD. The diagnosis seems more common in young males similar to observations in adult SQTS patients. This may reflect protection from ultra-short QT intervals in

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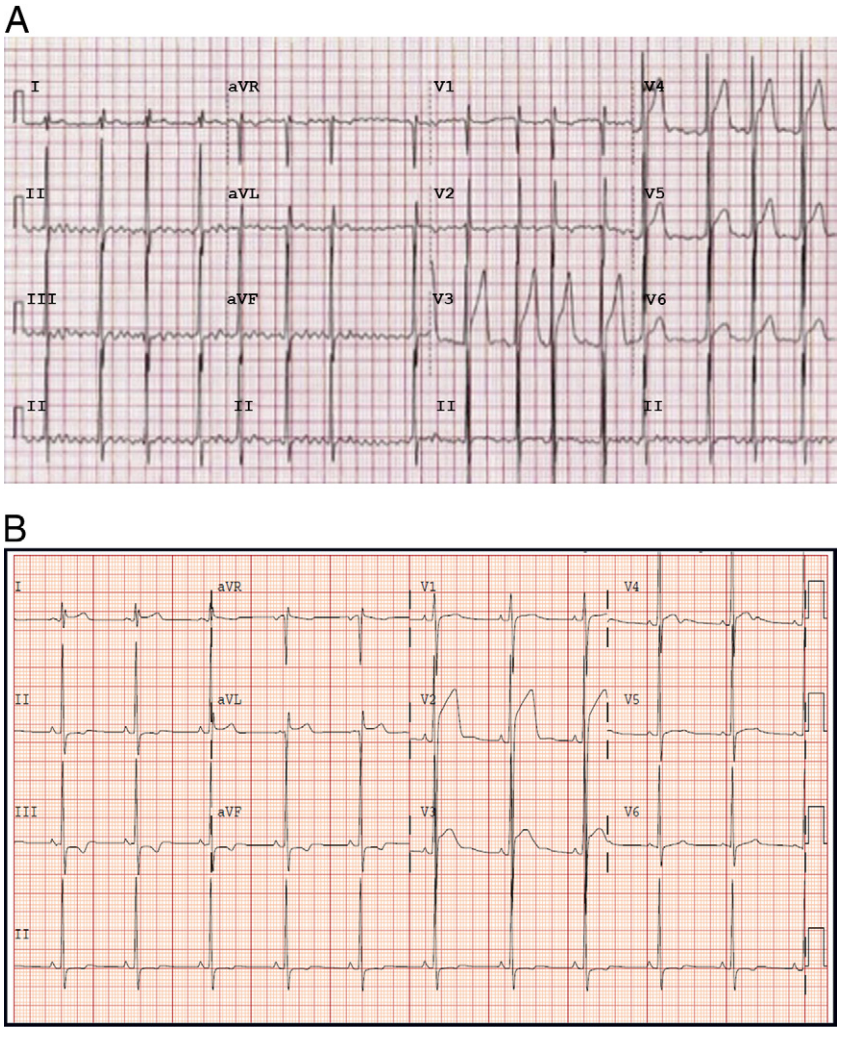

Figure 3 **Atrial Fibrillation and the Short QT Syndrome in a 17-Year-Old Young Male Resulting in Conversion to Sinus Rhythm and Prolongation of the QT Interval With Antiarrhythmic Therapy**

(A) 12-lead ECG of a symptomatic 17-year-old young male with atrial fibrillation. There is a short QT interval (QT interval: 320 ms, QTc interval: 355 ms), peaked T waves, and early repolarization. **(B)** After treatment with dofetilide and digoxin, there was prolongation of the QT interval (QT interval: 380 ms, QTc interval: 380 ms). The patient remained asymptomatic and on sinus rhythm except for short bouts of atrial fibrillation.

women because of the QT prolonging effects of estrogen (29). A modified Gollob score may be useful in identifying patients at a higher risk of clinical events and may prove useful for risk stratification, although larger cohort studies are necessary. Although ICD therapy proved useful in some patients, it was fraught with inappropriate shocks. One of 2 appropriate ICD shocks occurred despite a low dose of quinidine. Quinidine monotherapy did not prove to be effective in treating atrial fibrillation.

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Key Words: arrhythmias ■ atrial fibrillation ■ short QT syndrome ■ sudden cardiac death.